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### Deposited in DRO:

26 May 2015

### Version of attached file:

Accepted Version

### Peer-review status of attached file:

Peer-reviewed

### Citation for published item:

Rubini, M. and Zaio, P. and Roberts, C.A. (2014) 'Tuberculosis and leprosy in Italy. New skeletal evidence.', *Homo : journal of comparative human biology.*, 65 (1). pp. 13-32.

### Further information on publisher's website:

<http://dx.doi.org/10.1016/j.jchb.2013.07.006>

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**Tuberculosis and leprosy in Italy.  
New skeletal evidence**

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Abbreviated title: TB and leprosy in the past

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**Abstract:** Tuberculosis (TB) and leprosy are infections caused by *Mycobacteria*. This paper documents new skeletal evidence in Italy from the Iron Age site of Corvaro (Central Italy; 5<sup>th</sup> century BE) and the Roman site of Palombara (Central Italy; 4<sup>th</sup> –5<sup>th</sup> century CE), and briefly reviews the extant evidence for these infections in Italy. The skeletal evidence for TB in Italy is more ancient than for leprosy, and is more common. The oldest evidence for both mycobacterial diseases was in the north of Italy, but this could be by chance, even if biomolecular models suggest a land route from the East to central Europe, especially for leprosy.

**Key words:** infectious diseases; Mediterranean basin; Iron Age; Roman Period

## Introduction

Tuberculosis (TB) and leprosy are two of the most common and devastating infectious diseases in human history. TB is also common today, and is caused by various members of the *Mycobacterium tuberculosis* complex (MTBC). The principal cause of human infection is *M. tb* (Robbins and Cotran, 2002; Cooper, 2009). The other main bacterium responsible for TB in humans is *M. bovis*, which has a wider host range and is the main cause of the disease in other animals (Grange, 2008). Other members of the MTBC include the human pathogens *M. canettii*, *M. africanum*, and species habitually associated with animal infection, such as *M. microti*, *M. caprae* and *M. pinnipedii*. Today the distribution of TB is not uniform across the globe; about 80% of the population in many Asian and African countries is positive for tuberculin tests, while only 5-10% of the U.S. and European populations test positive (WHO, 2011). *M. tb* is usually contracted via the lungs and droplet spread (Dye, 2008), while *M. bovis* is transmitted to humans in the gastrointestinal tract via infected food products such as meat and milk (O'Reilly and Daborn, 1995; Robbins and Cotran, 2002). Most tuberculous infections in humans result in an asymptomatic, latent infection, and about one in ten latent infections eventually progresses to active disease; if left untreated, TB kills more than 50% of its victims (Robbins and Cotran, 2002). The classic clinical signs and symptoms are a chronic cough with blood-tinged sputum, fever, night sweats, and weight loss, the latter giving rise to the formerly prevalent colloquial term "consumption". Between the different modalities of expression, TB may also affect some bones and joints. Skeletal tuberculosis is, almost without exception, a result of haematogenous spread of infection from soft-tissue foci. Skeletal disease occurs only in a minority of instances; data from the pre-antibiotic era indicate that about 3-5% of cases showed bone changes (Robbins and Cotran, 2002; Ortner, 2003; Rubini, 2008a). Classically, the bone changes used to identify tuberculosis in osteoarchaeological remains are the characteristic lytic lesions showing little perifocal reactive bone in the vertebral bodies and large joints (Ortner, 2003; Rubini, 2008a).

Leprosy (or Hansen's disease) is a chronic infectious disease caused by *M. leprae*, an acid-fast, rod-shaped *bacillus* belonging to a single species with limited genetic variability (Monot et al, 2005). It has four types and 16 subtypes of single-nucleotide polymorphism (SNP) permutations (Monot et al. 2009). Leprosy is contracted by inhalation of bacteria-laden droplets from the lungs of an infected person. The incubation period can be very long (in some cases 20 years) before clinical signs and symptoms become apparent (Robbins and Cotran, 2002, Nunzi and Massone, 2009). Leprosy can affect all age groups and both sexes. Some of the signs that occur include relatively

painless ulcers, skin lesions consisting of hypo-pigmented macules (flat, pale areas of skin), and eye damage (dryness, reduction in the blinking reflex). Later there may be involvement of the hand and foot bones, with absorption, and facial disfigurement can develop due to the facial bones being affected (Robbins and Cotran, 2002; Nunzi and Massone, 2009). The response to the disease is highly variable. The immune status of each infected individual determines the type and severity of pathological changes (Nunzi and Massone, 2009). At one end of the immune spectrum there is low resistance to infection or multibacillary (MeSh-lepromatous) leprosy; at the other, there is high resistance to the infection, resulting in paucibacillary (MeSh-tuberculoid) leprosy (Kumarasinghe et al., 2005, Nunzi and Massone, 2009). However, they may help a clinician to place the patient in the more detailed Ridley-Jopling immune spectrum classification (Ridley and Jopling, 1966). Between these extremes are the borderline types. In addition to these groups that manifest clinical leprosy, individuals may be infected with the bacteria without developing the clinical signs of the disease. This is termed subclinical leprosy (Robbins and Cotran, 2002, Nunzi and Massone, 2009). According to some authors (e.g. Giannetti, 2001; Kumarasinghe et al., 2005, Kampirapap, 2008) the incidence of subclinical leprosy is high today, as it likely was in the past (Manchester, 1984). Although multibacillary leprosy is the most infectious form, especially in the historic past but also today where poor living conditions and diets exist, and paucibacillary leprosy the less infectious, in a general view of the disease is important to consider also the infectivity of the other forms of leprosy (Kampirapap, 2008), because in ancient times these probably played an important role in the spread of the disease (Manchester, 1984; Rubini and Zaio, 2009). According to official reports received “during 2011 from 130 countries and territories, the global registered prevalence of leprosy at the beginning of 2011 stood at 192,246 cases, while the number of new cases detected during 2010 was 228,474, excluding the small number of cases in Europe” (WHO 2012).

It is suggested that the decline of leprosy in the western world in the past was not monocausal but due to a complex web of causes: social, legal, political and bio-medical (Rawcliffe 2006). The latter is explained by the rise in TB. Studies that began in the 20th century proposed a model of cross-immunity between these two *Mycobacteria* as a possible cause of the decline of the leprosy.

The origin of this cross-immunity is controversial, but one fact is certain: in clinical contexts leprosy may be prevented following Bacillus Calmette-Guerin (BCG) vaccination in 20-91% of individuals, based on different studies (Merle et al. 2010). However, research on skeletal samples, albeit limited, has more recently refuted the hypothesis that this cross-immunity exists, and suggested an alternative explanation for the decline of leprosy in Western Europe (Donoghue et al.

2005). Furthermore, Manchester (1984) and Donoghue et al. (2005) suggested that immunological changes seen in multi-bacillary leprosy (lepomatous/low resistance), together with the socioeconomic impact of the disease, may have led to increased mortality due to TB, which resulted in the decline of leprosy. Despite this long history of epidemiological, clinical and microbiological studies the exact relationship between TB and leprosy still remains unclear. The only certain fact is that there is homology between the two *Mycobacteria* and that in Europe during the Middle Ages an increase of TB coincided with a decline in leprosy.

The aim of this study was to describe new skeletal evidence for TB and leprosy in Italy from two sites in Central Italy.

## **Materials and Methods**

The first skeleton to be described was excavated in the prehistoric site of Corvaro (Rieti), located in Central Italy and dated to the 5<sup>th</sup> century BE (Fig.1). This particular cemetery is a tumulus with a diameter of 50 meters and a depth of 3.70 meters, and probably was one of the cemeterial areas of the Aequi population. According to studies of this site (Alvino, 1989), it was used uninterruptedly for almost a thousand years (9<sup>th</sup>-2<sup>nd</sup> century BCE). The total number of tombs there was 361, and the graves were furnished with grave-goods typical of the period (Alvino, 1989). The tombs are all single and primary. Both sexes are well represented as subadults but the exact sex ratio at this moment is not possible because the complete anthropological study is still in progress. In tomb n. 109 (dated by grave-goods consisting of pottery and metal objects) an individual with pathological changes of the spine was discovered. The skeleton was almost complete but not well preserved (Fig. 2).

The second skeletal sample to be described came from the site of Palombara Sabina, located about 25 km to the north-east of Rome along the Via Salaria (Fig.1). In the early 90s, the site was explored and a large *villa* dated to the Roman republican period (4<sup>th</sup>-3<sup>th</sup> century BE) was located. This was reused during the Roman imperial period (2<sup>th</sup>-5<sup>th</sup> century CE). Within the structures, dated to the 4<sup>th</sup>-5<sup>th</sup> centuries CE, a large room was discovered with chaotic and disarticulated skeletal remains. This tomb could be a common grave with primary burials disturbed by environmental and anthropic factors. The condition of the bones is very good, but in some cases they are very fragmentary. The minimum number of individuals was estimated to be 47 adults and 7 non-adults (total number 54 individuals), based on the most frequently occurring bone (left ulna). Furthermore,

the presence of male and female hip bones suggests that both sexes were represented among the adults,. Near this room there was a “cappuccina” tomb, still sealed with mortar. This is the typical and most frequent tomb present in Italy during the Roman period. It was built with ceramic tiles leaning against each other and resting on the ground covering the body. Within this tomb only the upper limb bones of an adult individual were found. The economy of this site was typically agricultural and the population was poor, according to suggestions and studies of archaeologists (Mari and Moschetti, 1992). Calibrated radiocarbon dates for three similar bones (right humerus) provided a date of CE 475  $\pm$ 25 years (Rubini, 2008b). Three individuals, represented only by the rhino-maxillary portions of their skull, displayed pathological bone changes.

The methods used to estimate sex and age at death were those documented in the standard of Buikstra and Ubelaker (1994). For the recording of tuberculous bone changes, the suggestions of Robbins and Cotran (2002), Roberts and Manchester (2005) and Rubini (2008a) were used, while the recording of leprosy bone changes was based on Møller-Christensen (1967, 1969), Andersen and Manchester (1992), Roberts and Manchester (2005) Nunzi and Massone (2009) and Manchester (2012).

## **Description of the skeletons**

### **Corvaro**

Individual n. 109 was female and aged about 20-22 years. From an accurate examination of the entire skeleton some pathological changes on the costo-vertebral district were underlined. The spine showed collapse of the vertebral bodies. Kyphosis was present in the thoracic region (Fig. 3A,B), while in the lumbar region there was hyperlordosis, perhaps as a compensatory mechanism (Figure 3A). On the left lateral surface of the vertebral body of T5, a circular-shaped bony *sequestrum* of probable granulomatous origin with irregular margins and pitted internal surface was present (Fig. 4). The bodies of T6 and T7 show collapse of their anterior parts and were fused, displaying a wedge shape, and accompanied by bone formation (Fig. 5). The right 7<sup>th</sup> rib was fused to T6 and T7 (Fig. 6), and T9 and T10 were also collapsed and fused (Fig. 7). L3 showed bony loss on the antero-superior surface of the body which was also wedge-shaped (Fig. 8). Furthermore, L4 and L5 were also fused. In this last case only their posterior parts can be observed because of post-mortem damage located in the anterior portions (Fig. 9).

## **Differential diagnosis**

Differential diagnoses of the spinal lesions included neoplastic and infectious diseases, such as TB (Ortner, 2003; Roberts and Buikstra, 2003), osteoporosis, and fractures to the vertebral bodies (Rubini, 2008a). Other infections that can involve the spine include brucellosis and actinomycosis (Robbins and Cotran 2002; Ortner, 2003; Rubini, 2008a).

Brucellosis is a highly contagious zoonosis and is caused by ingestion of milk or meat from infected animals, or through close contact with their secretions. Transmission from human to human, through sexual contact, or from mother to child is rare, but possible (Robbins and Cotran 2002). The symptoms are like those associated with many other febrile diseases, but with an emphasis on muscular pain and sweating. The duration of the disease can vary from a few weeks to many months or even years. In the first stage of the disease, septicaemia occurs and leads to the classic triad of undulant fevers, sweating and migratory arthralgia and myalgia (Robbins and Cotran, 2002). If untreated, the disease can become chronic. Bone and joint changes of brucellosis can occur, and spondylodiscitis of the lumbar spine, accompanied by sacroiliitis, is very characteristic of this disease (Stäbler and Reiser, 2001). Furthermore, osteophytosis of the anterior part of the vertebral bodies can occur. Thus, this disease can be excluded as an explanation for the bony lesions in this skeleton because they do not fit the pattern expected.

Actinomycosis affects the cervicofacial area, but the spine can also be involved. When the facial bones are affected, the mandible rather than the maxilla is more often affected (Ortner 2003, Rothschild et al., 2006). The lesions are spherical in shape and large (Rubini, 2008a), and therefore actinomycosis is also excluded here. Metastatic cancer can also involve the spine, but it principally affects the pedicles of the vertebrae before the body (Ortner, 2003; Rubini, 2008a). In this skeleton the pedicles were not involved – so neoplastic disease is excluded. Fractures of the vertebral bodies are also excluded because no evidence was seen on the radiograph (Fig. 3B). Osteoporosis, or a reduction of bone mass, can also produce vertebral collapse because of demineralization of the bone (Robbins and Cotran, 2002). In this case the young age of the individual and the radiological evidence (Fig. 3B) exclude the presence of osteoporosis, because it usually affects older people.

Given the expression and distribution of the bony changes, the most likely diagnosis is Pott's disease (TB of the spine) with multiple lesions that involved many vertebrae. When considering destruction of the intervertebral disks (T6-T7, T9-T10 and L4-L5), the disease could be considered chronic, because destruction of the disk led to diffusion of the infection to the inferior and superior vertebral bodies (Rubini, 2008a).



## Palombara

The first sample is represented only by the portion of the maxillary region comprising the palate and piriform aperture, which is incomplete in its superior part (Fig. 10). The skeletal remains are attributable to an adult (laboratory code PLA). It showed the following bone changes: osteolysis limited to the piriform aperture areas with rounded and pitting of the margins; the alveolar region of the central incisors showed ante-mortem loss of bone; the anterior nasal spine displayed erosion and was capped with new bone formation; the hard palate had extensive pitting, probably of a chronic inflammatory nature (Fig. 11).

The second individual was represented by part of the left maxilla (Fig. 12), and was attributed to an adult (laboratory code PLF). The margin of the inferior nasal aperture was completely rounded and re-modelled, with traces of erosion and new bone formation and pitting. The alveolar area of the central incisors showed ante-mortem loss of bone. Because of poor preservation, it was not possible to know whether the nasal spine was present or not.

The third individual was represented by part of the right maxilla (Fig.13). The skeletal remains are attributable to an adult individual (laboratory code PLE). The margin of the nasal aperture was rounded and re-modelled. The bone loss involved the alveolar region associated with the first and second incisors and canine. Furthermore, slight pitting is present. The nasal spine appeared reduced in size and was capped with new bone formation. The residual surface of the hard palate showed extensive fine pitting (Fig.14).

Furthermore, it could be interesting to note in the disarticulated postcranial skeletal remains the presence of some bones with probable infectious changes. The first is a 2<sup>nd</sup> metatarsal bone (Figure 16 A, a, a1) that shows an abscess of circular shape with rounded margins in the medial proximal end. The *focus* is surrounded by an ivory bony ring. The second is a 3<sup>rd</sup> metacarpal bone (Fig. 15 B) that displays an abscess of rounded shape with well defined margins in the medial distal end. The third is a fragment of tibia (Fig. 16) with clear traces of periostitis and cortical thickening limited to the middle-shaft. The main problem is that because of the chaotic situation of the bones these districts were not attributable to any of the three samples described here.

## Differential diagnosis

There are various disease processes that could lead to bone changes in the rhino-maxillary region (Ortner, 2003). These include granulomatous diseases such as sarcoidosis and treponematoses,

fungal infections such as aspergillosis and mucormycosis (phycomycosis), actinomycosis (a bacterial rather than a true fungal disease), *lupus vulgaris* (tuberculosis of the facial skin and other soft tissues), and leprosy. Sarcoidosis is a granulomatous disease of unknown aetiology. Like leprosy, it tends to affect the phalanges of the hands and feet, causing lytic lesions and no reactive bone formation (Ortner, 2003). However, in the skull it mainly causes destruction of the internal surfaces of the nasal bones and never produces erosion and new bone formation on the margins of the nasal aperture (Robbins and Cotran, 2002). Thus, this disease can be excluded as an explanation for the bony lesions in the skeletal remains described here. Treponemal diseases should also be discussed since, like leprosy, they can lead to destruction of the nasal bones (Ortner, 2003). They are syphilis (venereal and endemic), yaws and pinta. The granulomatous infection is caused by spirochetes of the genus *Treponema*. Excluding pinta, which does not affect bones, these diseases in the tertiary stage can involve the skeleton. Inflammatory bony changes with a large bone formation can be present. This produced an alteration of normal bone morphology (Robbins and Cotran, 2002; Ortner, 2003). These changes can be specific, such as gummatous lesions, or non-specific non-gummatous lesions such as periostitis, osteitis and osteoperiostitis. The destruction of the rhino-maxillary area can occur, but it is very rare (Robbins and Cotran, 2002). In yaws the final stage of the infection can be characterized by widespread bone, joint and soft tissue destruction, which may include extensive destruction of the bone and cartilage of the nose (rhinopharyngitis *mutilans* or 'gangosa'). Bejel (endemic syphilis) is a disease present today in desert regions of Africa, Middle East, central Australia and Asia. The involvement of the skull is very rare, with gummas of the soft palate and nose developing in the final stage (Robbins and Cotran, 2002). 'Gangosas' may occur very rarely. In venereal syphilis numerous bones in the body may be involved. According to Ortner (2003), the cranial changes are the main features for a correct diagnosis on osteoarchaeological remains. The teeth may be involved in congenital syphilis (e.g. Hutchinson's incisors – Robbins and Cotran, 2002). Syphilis could produce also the characteristic "saddle nose" with enlargement of the nasal cavity. However in this case the margins of the pyriform aperture do not display erosion with new bony formation (Rubini, 2008a). In contrast with leprosy the nasal spine is spared (Rogers and Waldron, 1989) and anterior alveolar bone lesions are very rare (Møller-Christensen, 1967 p. 297). Therefore, the skeletal changes in these skeletons do not correspond to those of the treponemal diseases. Aspergillosis is marked by inflammatory granulomatous lesions in the skin, ear, orbit, nasal sinuses, lungs, and sometimes the bones and meninges. It affects the paranasal sinuses and orbits or the anterior cranial fossa (Robbins and Cotran, 2002). Mucormycosis (phycomycosis) is a

fungal disease. The district mostly affected is the nasal area in particular the walls of the paranasal sinus (Ortner, 2003). This rare fungal infection was mainly described in individuals with unchecked diabetes (Ruoppi *et al.*, 2001). In these individuals a diagnosis of aspergillosis or mucormycosis can also be ruled out. Actinomycosis affects the cervicofacial area, and bone involvement is very rare. When affected, the mandible rather than the maxilla is more involved. Furthermore, it does not involve the nasal area (Robbins and Cotran, 2002; Ortner 2003; Rothschild et al., 2006); this was not the case for these individuals. *Lupus vulgaris* is a chronic tuberculous infection of the skin. Also in this case the destruction of the nasal bones can occur (Robins and Cotran, 2002). The anterior alveolar process, however, is rarely affected (Møller-Christensen, 1967), which discounts *lupus vulgaris* as a diagnosis.

Given the localization of the lesions in the three individuals under study, the most likely diagnosis is lepromatous leprosy (Møller-Christensen, 1967, 1969; Andersen and Manchester, 1992, Roberts and Manchester, 2005, Al-Tubaikh, 2010; Manchester, 2012). Osteological changes are present in the rhino-maxillary region. Partial resorption of the anterior nasal spine in PLA and PLE, along with enlargement and rounding of the piriform aperture and osteolysis of the inferior margin of the nasal aperture and of the alveolar margins are the bone changes seen in these individuals and in leprosy (Roberts and Manchester, 2005; Nunzi and Massone, 2009). Furthermore, the presence of pitting in all individuals indicates probable chronic inflammation of the naso-palatal region. Also this could suggest a diagnosis of leprosy (Ortner, 2003; Nunzi and Massone, 2009, Manchester, 2012). According a recent protocol (Al-Tubaikh, 2010; Manchester, 2012) the presence of rhino-maxillary syndrome in osteoarchaeological remains could be pathognomonic of lepromatous leprosy. Indirectly also the changes present in the postcranial bones could support the presence of some infectious disease (leprosy?) in this human group. The abscesses present on the hand and foot bones could be an initial level of an infectious process situated in a skeletal districts involved in the leprous sensory neuropathy (Ortner, 2003; Nunzi and Massone, 2009; Manchester, 2012). In fact, cutaneous anaesthesia predisposes to trauma leading to “ulceration, secondary pyogenic bacterial invasion from external sources, and to deep tissue spread to bone and joint cavities, giving rise to osteomyelitis and septic arthritis” (Manchester, 2012). The presence of periostitis is not absolutely pathognomonic of the leprosy. Furthermore, it is an aspecific indicator, but it has often been observed as non-specific inflammatory changes in this pathology (Nunzi and Massone, 2009).

## Discussion

The history of TB and leprosy is very long. Both infections are caused by *Mycobacteria*. TB has been described in archaeological remains in Europe (for a survey see Holloway et al., 2011) and in Italy from the Neolithic period, while leprosy only from the Bronze Age (for a survey see Rubini and Zaio, 2009). At this moment, the most ancient real cases known in the world are: for TB an Eastern Mediterranean (Israel) Neolithic settlement dated about 9000 BP (Hershkovitz et al., 2008) while for leprosy there is a case found in India and dated 2000 BE (Robbins et al., 2009). Molecular studies have shown that both diseases started from Africa following the migration paths of the first human groups in the direction of Asia (Gutierrez et al., 2005; Monot et al., 2005). It has been shown that TB was widespread in Italy in the past (Fig. 17 and Table 1). The most ancient evidence comes from two Neolithic skeletons found in the Northwest, in the region of Liguria (Formicola et al., 1987; Canci et al., 1996).

Skeletal evidence for leprosy in Italy is very scarce (Fig. 18 and Table 2). Currently, the oldest example has been described from the northeastern part of the country, at Casalecchio di Reno (Mariotti et al., 2005). During the Roman period there was also evidence reported from central Italy, in a skeleton of a child from a cemetery located near Rome (Rubini et al., 2012a). In the early Middle Ages there are three individuals from central Italy, from the Morrione cemetery (7<sup>th</sup>-8<sup>th</sup> century CE) in Molise (Belcastro et al., 2005; Rubini and Zaio, 2009), while in the late mediaeval period (13<sup>th</sup> century) there are two skeletons with evidence of leprosy, both from southern Italy (Fornaciari et al., 1999; Rubini et al., 2012b).

Our case of Tb came from a site located in central Apennines. During the 7<sup>th</sup>-5<sup>th</sup> centuries BE these mountain sites were partially isolated under the genetic aspect, probably for geographic reasons (Rubini et al., 2007). The demographic aspect of these communities shows (as in the case of Corvaro) a long period of survival but without relevant demographic increases up to decline (Rubini, 2010). Furthermore, they showed a strong endogamy that constituted the base of social subdivision in kinship structures (Rubini, 1996). Probably this isolation was not commercial, as is demonstrated by presence of some objects that came from other territories, for example Etruria. The presence of TB in the prehistoric site of Corvaro is very interesting because at this moment it is the first described in this region. The fact that in this cemetery only one case among 361 individuals (0,3%) was found is certainly casual, also considering that cases of pulmonary TB are very difficult to diagnose (Santos and Roberts, 2006). Surely there is an under-representation of the problem. The other consideration was that this was not a commercial site with great passage of people, as for

example the coeval Tyrrhenian coastal sites of the *Latium* or Etruria but a simple rural site located in an Apennine valley (Alvino, 1989). This fact suggests that the contagion was casual and linked probably to the small traders who passed through Corvaro, especially during the good season because of the presence of snow during all the winter, which renders the transit of the paths difficult on the Adriatic side. A further observation was that a highly contagious and mortal disease like TB did not constitute a serious danger for the health of this community, which survived uninterruptedly for another three centuries without a relevant demographic fall (Rubini, 2010). This last observation seems in accord with the hypothesis of Manchester (1984) about the link between increase of the population density and TB. On the Corvaro site the population density was linear during its long existence. There is no peak of demographic increase, and the number of the people that lived there was very low in comparison with the coeval coastal centers of the Adriatic and Tyrrhenian side of the Central Italy (Rubini, 2010). Probably it was this circumstance that did not produce an epidemiological event with damage to the demographic asset of the community.

The cases of leprosy come from a very poor rural site (Mari and Moschetti, 1992). Also the general condition of health of the Palombara community is very poor (Rubini, 2008b). The Palombara skeletal population shows many disfigurant individuals, in part because of infectious diseases like these cases of leprosy and in part because of traumas or genetic pathologies (Rubini, 2008b). This particular community of those “touched by God” probably during the 5<sup>th</sup> century CE lived in a great isolation under the commercial and productive aspect, the little pottery found in the site is all of local production (Mari and Moschetti, 1992). We don’t know if this condition was free or compulsory. It may be considered certain that they carried out a productive activity that was very poor but perhaps dignified with respect to their terrible and inhuman conditions of life and overall health. According to some authors leprosy is a disease that in the past (Manchester, 1984; Manchester and Roberts, 1989) like today (Kerr-Pontes et al., 2004) is present on rural sites and for this reason declined with the urbanisation phenomenon. Even today countries with an important presence of leprosy, like India and Brazil, show a greater incidence of the disease in their rural regions (WHO, 2012).

The study of the presence and spread of these infections is very difficult although very interesting and important for charting their origin and history. The difficulties (such mentioned above) derive from the fact that the diagnosis of TB in absence of Pott’s disease is problematic, as the bone changes are non-specific and could be caused by other diseases. The presence of rib lesions is not sufficient for a reliable diagnosis (Santos and Roberts, 2006), and the joint changes present the

same problems in interpretation. Furthermore, the skeleton is affected only in 3-5% of the cases (Ortner, 2003). Biomolecular analysis is an important way forward for the diagnosis of TB, but at present the time and cost for this type of analysis is prohibitive for many scholars working in palaeopathology. However, to date, ancient pathogen DNA analysis has focused most on TB diagnosis, mainly to confirm skeletal changes (for example: Mays et al., 2001; Mays et al., 2002; Hershkowitz et al., 2008). A population-based study in palaeopathology using biomolecular analysis is at the moment not practical, but in the future as costs reduce and reliability improves more work using this type of analysis will become possible. The same problem is present for diagnosing leprosy. It is possible to diagnose leprosy only in the presence of pathognomonic rhino-maxillary or hand and foot bone changes. Leprosy affects the bones only in the chronic final stages, and not always, because again it also only affects 3-5% (Nunzi and Massone, 2009). It is obvious that in the absence of relevant skeletal signs, the disease can only be diagnosed using biomolecular analysis, as with TB, but the same problems outlined above apply here. Furthermore, in some cases a failed analysis is also possible for various reasons (Rubini et al. 2012a). In conclusion, the skeletal evidence for TB and leprosy is certainly under-represented in Italy and probably not only there. However, this under-representation is also linked to the random nature of discovery and excavation of human remains, their preservation, and their chronology and geographic location.

## **Conclusions**

The presence of skeletal TB in Italy is more ancient than leprosy, and skeletal evidence for the former is more common. The skeletal evidence for leprosy at present is very scarce. This new evidence could enrich the scanty documentation of leprosy. Both diseases show their most ancient evidence in the north, but this fact could be by chance. However, although many skeletal collections have been studied in Sicily (Rubini et al., 2001), at this moment there is no evidence of leprosy or tuberculosis there. The particular location of this island in the Mediterranean has always represented an important crossroads for people, genes, diseases and cultures between the Near East, Africa and Italy (Rubini et al., 1999; Cavalli Sforza et al., 2005; Rubini and Mogliazza, 2006). The absence of these diseases in ancient Sicily could suggest the hypothesis that TB and especially leprosy preferred a terrestrial pathway of transmission from the East to the Europe. With regard to leprosy, a similar model of spread was proposed on a biomolecular basis by Monot et al. (2005). In the future

more skeletal data for these two infectious diseases and extensive application of newer analytical techniques (e.g. biomolecular analysis) could be helpful in understanding the dynamics (increase, spread, possible cross-immunity and decline) of these diseases in ancient times.

**Acknowledgements** - We would like to thank: Vittorio Cerroni, Scientific Technical Assistant of the Anthropology Laboratory of the S.B.A.L., for the graphic creations and figures and Archer Martin archaeological supervisor in American Academy of Rome for the English revision.

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## Caption figures and tables

### Figures

- 1- Location of Corvaro and Palombara
- 2- Diagram of individual n.109 (grey = bones present)
- 3 – Corvaro T109. A) Spine with kyphosis present in the thoracic region while in the lumbar region there is a hyperlordosis. B) Radiograph of the spine with lytic lesions due to the infection
- 4- Corvaro T109. Left lateral surface of the vertebral body of T5 with a circular shaped bony *sequestrum* of probable granulomatous origin.
- 5- Corvaro T109. The bodies of T6 and T7 are fused in their dorsal parts, displaying a wedge shape, with bone formation.
- 6- Corvaro T109. The right 7<sup>th</sup> rib is fused to T6 and T7, and extensive pitting is present on the dorsal aspect of the rib.
- 7- Corvaro T109. T9 and T10 collapsed and fused together.
- 8- Corvaro T109. L3 with erosion on the antero-superior surface of the wedge shaped body
- 9- Corvaro T109. Fused L4 and L5; their anterior parts are damaged post-mortem.
- 10- Palombara. Individual PLA with absorption and pitting on the margins of, and around, the nasal aperture. The alveolar bone in the region of the central incisors shows loss of bone antemortem.
- 11- Palombara individual PLA. Oral palatal view of PLA with extensive pitting.
- 12- Palombara individual PLF. View of the margin of the nasal aperture which is remodelled with traces of erosion and new bone formation and pitting.
- 13- Palombara individual PLE. View of the margin of the nasal aperture which is remodelled. Bone loss is present on the alveolar bone associated with the first and second incisors and canine teeth, with evidence of pitting.
- 14- Palombara individual PLE. Oral palatal view that shows extensive fine pitting.
- 15- Palombara. A) 2<sup>nd</sup> left metatarsal bone with abscess to rounded margins in the medial proximal end a, a1) Stereomicroscopic vision (10x); B) 3<sup>rd</sup> right metacarpal bone with rounded shape in the medial distal end.
- 16- Fragment of left tibia with traces of periostitis and cortical thickening
- 17-Location of sites in Italy with the presence of TB in skeletal remains (the numbers correspond to the cases listed and described in table 1)
- 18- Location of sites in Italy with the presence of leprosy in skeletal remains (the numbers correspond to the cases listed and described in table 2)

### Tables

- 1-Evidence of TB in Italy from published literature, with new evidence
- 2- Evidence of leprosy in Italy from published literature, with new evidence



Figure 1

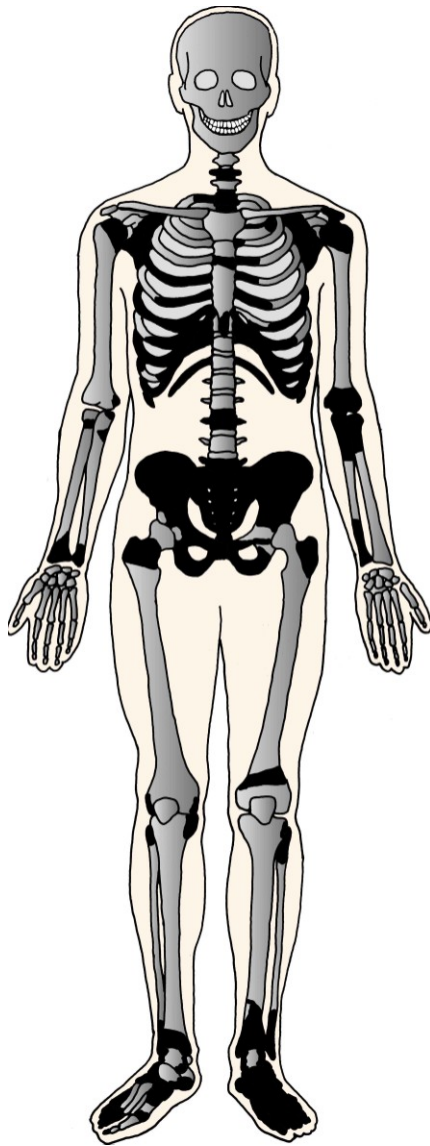


Figure 2



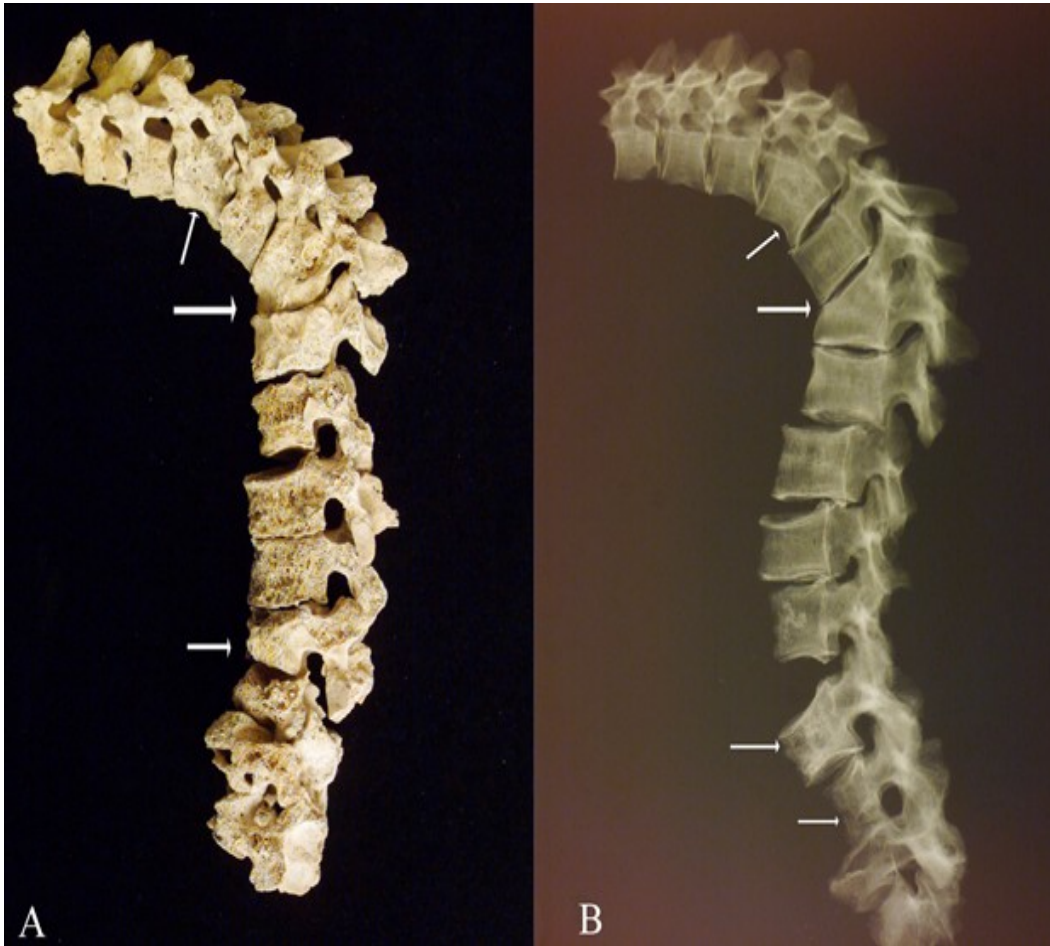


Figure 3



Figure 4



Figure 5



Figure 6



Figure 7



Figure 8





Figure 9



Figure 10





Figure 11



Figure 12

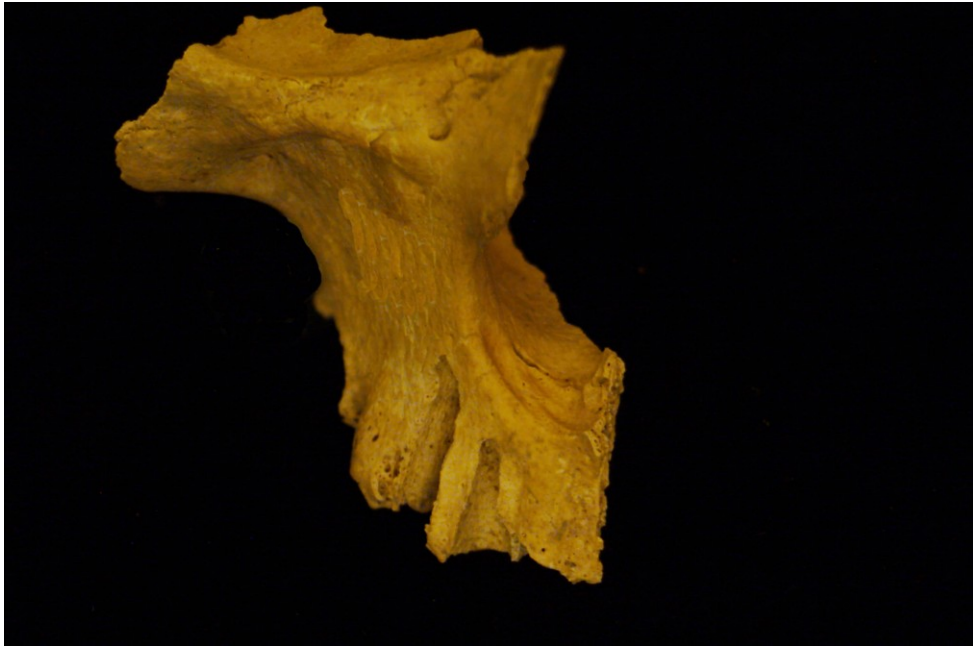


Figure 13



Figure 14

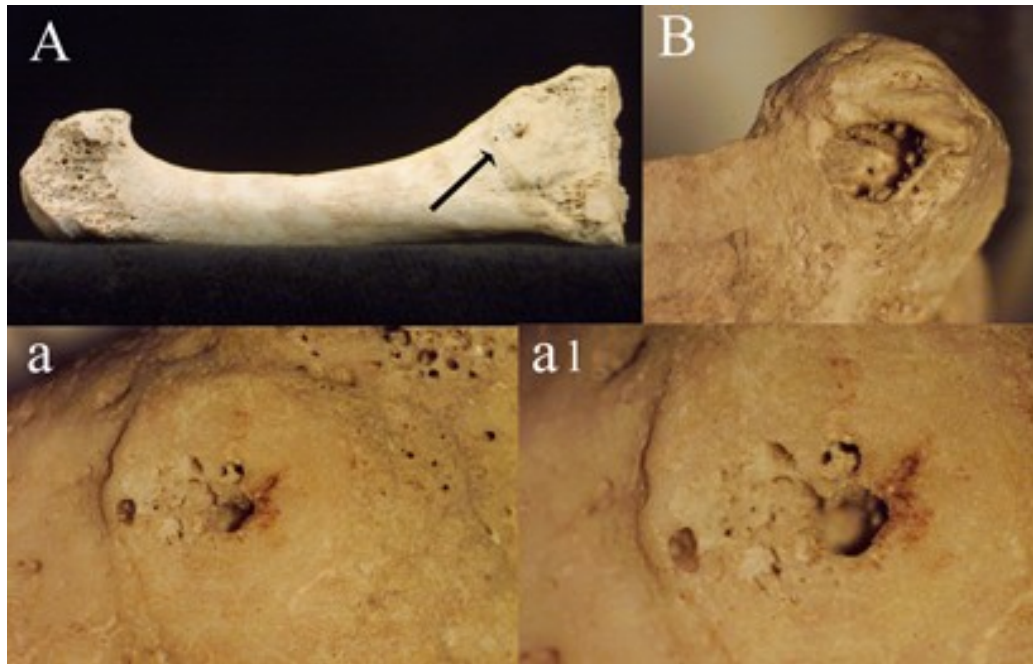


Figure 15



Figure 16



Figure 17





Figure 18



Table 1

	Site	Chronology	Case	Literature
1	Grotta dell'Arma dell'Aquila (Savona, NW Italy)	C14 date: 5800±90 years BP	Female, c. 30 years old: Pott's disease.	Canci et al., 1996.
2	Arene Candide (Savona, NW Italy)	C14 date: 1st half of 4 <sup>th</sup> millennium BE	Male, 15 years old: Pott's disease.	Formicola et al., 1987.
3	Olmo di Nogara (Verona, NE Italy)	16th–12th century BE	Male, c. 40-45 years old: Pott's disease Male, 25-30 years old: Pott's disease	Lucatello., 2006-2007.
4	Madonna di Loreto (Trinitapoli, Foggia SE Italy)	16th century BE	Adult male: Pott's disease.	Canci et al., 2001.
5	Alatri (Frosinone, Central Italy)	18th-16th century BE	Male, 32-38 years old: vertebral (Pott's disease?) and tuberculous lesions distal femoral epiphysis	Sallustio et al., 2004.
6	Preda Zedda (Nuoro, Sardinia)	12th-10th century BE	Adult female: Pott's disease.	Germanà, 1982.
7	Corvaro (Rieti, Central Italy)	5th century BE	Tomb 109: Male, c. 35-40 years old: Pott's disease.	Present study
8	Pozzuolo (Siena, Central Italy)	Etruscan period (7 <sup>th</sup> -2 <sup>nd</sup> century BE?)	Female, 25-40 years old: Pott's disease.	Pietrangelo & D'anastasio, 1997.
9	Ercolano (Pompei, SW Italy)	79 AD	Male, 35-40 years old: Pott's disease, rib periostitis; Female, 30-35 years old: Pott's disease and rib periostitis	Thillaud and Grmek 1987; Di Domenicantonio et al., 1999; Capasso and Di Tota, 1999; Capasso et al. 2000; Capasso, 2001; Capasso, 2007
10	Rome (Central Italy)	1 <sup>st</sup> -2 <sup>nd</sup> century CE	Male, 25-35 years old: Pott's disease	Canci et al., 2005.
11	Mitza Salida (Masullas, Oristano, Sardinia)	1st -3rd century CE	Tomb 38, male adult :Pott's disease.	Manos and Floris, 2005.
12	Rome (Central Italy)	2nd -3rd century CE	Adult male: calcified mass in the chest; pulmonary tuberculosis?.	Cucina et al., 1999.
13	Nonantola (Modena, NE Italy)	12-14 century CE	Adult individual? Rib periostitis	Bertoldi et al., 2005.
14	Cangrande della Scala (Verona, NE Italy)	1291-1329 CE	Mummified remains male 38 years old. Pulmonary tuberculosis.	Fornaciari, 2006.
15	San Sebastiano (Saluzzo, Cuneo, NW Italy)	15-16 century CE	Tomb 85: female, 30-35 years old: rib periostitis. Tomb 20: Male, 40-45 years old: Pott's disease. Tomb 83: Male, 35-40 years old: Pott's disease.	Lippi et al., 2009.
16	Naples (SW Italy)	16 century CE	Male, c. 25 years old: nodular tuberculosis.	Fornaciari et al., 1987; Fornaciari et al., 1989.
17	Cardinal Carlo de' Medici (Firenze, Central Italy)	1595 – 1666 CE	Male 71 years old: Pott's disease	Giuffra et al., 2009.

Table 2

	Site	Chronology	Case	Literature
1	Casalecchio del Reno (Bologna, NE Italy)	5 <sup>th</sup> century BE	Adult male: rhino-maxillary and changes in tarsal bones	Mariotti et al., 2005
2	Palombara (Rome, Central Italy)	C14 475 $\pm$ 25 years CE (5 <sup>th</sup> century CE)		Present study
3	Martellona (Rome, Central Italy)	2nd-3rd century CE	Child about 4-5 years old: rhino-maxillary syndrome	Rubini et al., 2012a
4	Campochiaro (Campobasso, Central Italy)	6 <sup>th</sup> - 7 <sup>th</sup> century CE	Adult male: changes in tarsal bones Adult male and one adult woman: rhino-maxillary syndrome and changes in tarsal bones	Belcastro et al., 2005; Rubini and Zaio, 2009
5	Montecorvino (Foggia, SE Italy)	13 <sup>th</sup> -14 <sup>th</sup> century CE	Adult male: rhino-maxillary syndrome	Rubini et al., 2012b
6	Calabria (SW Italy)	13 <sup>th</sup> century CE	Adult male: rhino-maxillary syndrome	Fornaciari et al., 1999